DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08 July 2010 has been entered.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Drawings

3. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because:

a. The lettering is not of proper size, uniform density, and well-defined in Figure(s) 1-11. See 37 CFR 1.84 (l) and (p)(1) – (5). ("Numbers, letters, and reference characters must measure at least .32 cm (1/8 inch) in height.")

4. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The

corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 58-87 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

7. Attention is directed to MPEP 904.01.

> The breadth of the claims in the application should always be carefully noted; that is, the examiner should be fully aware of what the claims do not call for, as well as what they do require. During patent examination, the claims are given the broadest reasonable interpretation consistent with the specification. See *In re Morris*, 127 F.3d 1048, 44 USPQ2d 1023 (Fed. Cir. 1997). See MPEP § 2111 - § 2116.01 for case law pertinent to claim analysis.

8. It is noted with particularity that narrowing limitations found in the specification cannot be inferred in the claims where the elements not set forth in the claims are linchpin of patentability. *In re Philips Industries v. State Stove & Mfg. Co, Inc.*, 186 USPQ 458 (CA6 1975). While the claims are to be interpreted in light of the specification, it does not follow that limitations from the specification may be read into the claims. On the contrary, claims must be interpreted as broadly as their terms reasonably allow. See *Ex parte Oetiker*, 23 USPQ2d 1641 (BPAI, 1992).

9. Claim 58 is the sole independent claim pending and under consideration. Claims 58, 62, 67, 83, and 85 are representative, and, for convenience, are reproduced below.

58 (Previously presented): A method of sequencing a target polynucleotide comprising:

(a) extending a primer annealed to said target polynucleotide utilizing a labeled nucleotide wherein the label is attached to the nucleotide via a cleavable linkage;

(b) determining whether said labeled nucleotide is present within said extended primer by detecting said label, wherein the presence of said labeled nucleotide within said extended primer is correlated to the sequence of said target polynucleotide;

(c) cleaving said label from said nucleotide; and

(d) repeating steps (a)-(c).

62 (Previously presented): The method of claim 59, wherein said quencher moiety is an optionally substituted phenyl, naphthyl, anthracenyl, benzothiazole, benzoxazole, benzimidazole, pyrene, anthracene, naphthalene, acridine, stilbene, indole, benzindole, oxazole, thiazole, 4-amino-7-nitrobenz-2-oxa-1,3-diazole, cyanine, carbocyanine, carbostyryl, porphyrin, salicylate, anthranilate, azulene, perylene, pyridine, quinoline, coumarin, polyazaindacene, xanthene, oxazine, benzoxazine, carbazine, phenalenone, benzphenalenone, 4-bora-3a,4a-diaza-s-indacene, fluorophorescein, rhodamine, rhodol, 5-carboxyfluorophorescein (FAM), 5-(2'-aminoethyl) aminonapthalene-1-sulfonic acid (EDANS), anthranilamide, terbium chelate, Reactive Red 4, dabcyl, nitrotyrosine, malachite green, Texas red, dinitrobenzene, ATTO dye, EVO Dye, DYO Dye, Alexa dye, or BODIPY dye.

67 (Previously presented): The method of claim 66, wherein said fluorescent label is an optionally substituted pyrene, anthracene, naphthalene, acridine, stilbene, indole, benzindole, oxazole, benzoxazole, thiazole, benzothiazole, 4-amino-7-nitrobenz-2-oxa-1,3-diazole, cyanine, carbocyanine, carbostyryl, porphyrin, salicylate, anthranilate, azulene, perylene, pyridine, quinoline, coumarin, polyazaindacene, xanthene, oxazine, benzoxazine, carbazine, phenalenone, benzphenalenone, 4-bora-3a,4a-diaza-s-indacene, fluorophorescein, rhodamine, rhodol, 5-carboxyfluorophorescein (FAM), 5-(2'-aminoethyl) aminonapthalene-1-sulfonic acid (EDANS), anthranilamide, terbium chelate, Reactive Red 4, Texas red, ATTO dye, EVO Dye, DYO Dye, Alexa dye, or BODIPY dye.

83 (Previously presented): The method of claim 58, wherein said target polynucleotide forms part of an array.

85 (Previously presented): The method of claim 58, wherein the sequencing is iterated or clocked by the action of a physical signal.

As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

<u>The quantity of experimentation necessary</u>

The quantity of experimentation necessary is great, on the order of several man-years, and then with little if any reasonable expectation of successfully enabling the full scope of the claims.

<u>The amount of direction or guidance presented,</u>

The amount of guidance provided is limited, generally prophetic, and not commensurate with the scope of the claims.

The presence or absence of working examples

Pages 67-75 of the disclosure are directed to "Examples," however, upon review of this section of the disclosure it is noted that none of the examples actually teach the sequencing of any one, much less a combination of target nuclei acids, be they DNA or RNA. (For purposes of examination, the term "sequencing" has been construed as requiring more than one nucleotide to be identified in series in a given target nucleic acid.)

Acknowledgement is made of the example appearing at the bottom of page 72 (last line) and bridging to page 75. While this example is entitled "Sequencing by synthesis with DNA polymerase on glass microarray surfaces," no actual sequence of nucleotides was determined. As noted on page 73, a reaction wherein ddNTP were incorporated was conducted and a detection step was performed so to see if any signal was present. The example also teaches the use of Exonuclease III to effect removal of the label from an incorporated nucleotide, but no subsequent incorporation of a labeled nucleotide as conducted/disclosed. Further, the method disclosed does not teach the use of FRET or of the listing of quenchers or fluorescent labels recited in claims 62 and 67.

The aforementioned example also teaches that the primers were arrayed to the support. In contrast, the specification teaches at page 45, last paragraph, that one can sequence directly from a complex mixture of nucleic acids. Such an embodiment is fairly encompassed by claim 83.

In accordance with claims 61, 62, and 65-67 numerous labels, including quencher moieties are recited. The specification has not been found to set forth reaction conditions under which each of these specified/claimed reagents are to be used in the claimed method whereby any number of nucleic acids are sequenced in solution or mixed together on a support in a simultaneous manner. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* (Fed. Cir. 1997) 42 USPQ2d 1001. As set forth in the decision of the Court:

> "'[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
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> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
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> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the

> novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

In order to fully enable not only the compounds and compositions explicitly recited, but additional compounds and compositions that are encompassed by independent claim 58, the public would have to engage in undue experimentation to not only find a workable method, but to also avoid and overcome the myriad operability issues recognized by applicant, *infra*

The predictability or unpredictability of the art

Applicant, at page 5 of the disclosure states:

> One disadvantage of sequencing with fluorescently labelled nucleotides is non- specific adsorption to surfaces. This is particularly problematic when single molecules are analysed and the template molecules are immobilised on a surface.

Applicant, at page 14, last full paragraph, states:

> The labelled nucleotides that are incorporated may be dNTPs or ddNTPs. The disadvantage of adding dNTPs is there is no absolute certainty as to how many fluorescent bases become incorporated at each cycle. The disadvantage of labelled ddNTPs is that although only one labelled base will be added, after detection and removal of this base, the nucleotide which replaces it needs to allow incorporation of the next fluorescently labelled nucleotide and therefore cannot be blocked at the 3' end. However, this may allow multiple bases to be incorporated. Therefore it is possible that more than one base may be added. This would shift the register beyond the last base that has been sequenced.

Applicant, at page 45, last paragraph, teaches:

> Although the invention can be carried out on a purified fragment of a polynucleotide, it offers particular advantages for sequencing polynucleotides directly from a complex mixture such as sheared/fragmented genomic DNA, a mRNA population or a population of fused mRNA-polypeptides.

Applicant, at page 56, teaches:

> The nucleotides that are available are not 100% pure. Often the other bases contaminate. Therefore where a labelled reaction gives a particular signal which would be expected to be due to a particular base, in a minority of cases this might in fact be due to a different base. This different base can incorporate at a low rate especially if nucleotides are in limiting concentrations.

The breadth of the claims

Applicant, at page 42, lines 13-16, state:

> Compared to the degree of parallelism currently available (96 Sanger sequencing reactions within individual capillaries on a state-of-the-art DNA sequencer) a whole wafer high-density oligonucleotide array has the capacity to analyse 60 million reactions (e.g. see www.perlegen.com website). (Emphasis added)

As set forth at page 11, lines 1-2, of the specification: "sequencing will involve incorporation of bases at consecutive positions which are separated from their labels by extraordinary long linkers" (emphasis added). It is noted with particularity that the claims (e.g., claims 63-65) do not require that the linkers be of any particular length, much less be "extraordinarily long."

Acknowledgement is made of claim 86 requiring the performance of wash steps. While not positively recited, it is assumed that the purpose is to remove any unincorporated or cleaved label. Given that claim 86 must further limit claim 58 from which it depends, and given that no other claim requires any wash step, the method of claims 58, and claims 59-85 and 87 which depend therefrom, have been construed as encompassing a method of sequencing whereby no unincorporated labeled nucleotide and/or cleaved label/reporter, is removed from the reaction mixture. As a consequence of al labels being present, one would not be able to readily determine which, if any, nucleotide(s) had been incorporated. In short, the method as claimed is

inoperable. It is noted that one cannot satisfy the enablement requirement for a method that is inoperable.

In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

Response to argument

10. Agreement is reached with applicant's representative where at page 11 of the response of 08 July 2010, it is asserted:

> Applicants respectfully maintain that the subject specification describes means for practicing the claimed method in regard to the cleaved label.

11. The issue at hand is not what the specification may generally "describe," but rather, what he specification fully enables.

12. While agreement is also reached in that there is no *per se* rule requiring any example, applicant is still, nonetheless, required to enable the full scope of that which is claimed, and that this full enablement requires the disclosure of specific reaction conditions and starting materials. Claims presently under consideration recite extensive *Markush* group of compounds and compositions. The specification does not set forth any reaction conditions for these required reactants. It is well settled that "when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art." *Genentech.*

13. At page 12 of the response applicants representative states:

> Applicants respectfully submit that the co-inventor's publication (Mir et al., Nucleic Acids' Research, January 2009, 37(1):e5) describes how three (3) contiguous bases of sequencing information are obtained using one of the detection schemes (microarray scanner) described in the subject specification using equipment available in a typical lab but without specific instrumentation for temperature or fluid control.

14. The above argument has been considered and has not been found persuasive. As an initial matter, it is noted that the disclosure is representative of work being reported some 6 years post effective filing date. Additionally, the level of disclosure in the article is not commensurate with that of the instant application.

15. While argument is presented that the method cam be practiced by hand and does not require various devices, such limitations, and in particular, exclusions, have not been read into the claims. As noted above claims are given their broadest reasonable interpretation that is consistent with the specification.

16. While attention is directed to various prior art publications that are asserted to teach the use of some of the claimed reactants, such document are not US patents and as such essential subject matter found therein cannot be incorporated by reference. Additionally, the specification is silent as to how prior art methods are to be adapted to result in full enablement of the alleged novel and non-obvious method being claimed.

Conclusion

17. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action

after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

18. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571)272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

20. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634